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Add on Acebrophylline and QoL in Smoker Asthmatics

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Abstract

***Aims and Objectives:** The present study was carried out to assess whether smoking alters quality of life (QoL) in asthma patients and if so, can it be counteracted by add on acebrophylline in them.*

***Material and Methods:** One hundred fifty smokers and 75 non-smoker, adult asthma patients, of either sex were enrolled for the study. Smoker patients were further divided in 2 groups. Test group I (TG1) patients received "Add on acebrophylline" along with inhaled corticosteroids(ICS) and long acting beta 2 agonists (LABA) but test group II (TG2) patients received "Add on placebo" along with inhaled ICS and LABA. Nonsmoker asthma patients served as controls and received drugs similar to TG2 patients. Control of asthma and Quality of life (QoL) in them was assessed using mini Asthma Quality of Life Questionnaire (Mini AQLQ) and Asthma Control Questionnaire (ACQ) on Day 0, Day 15 and Day 30.*

***Results:** It was observed that cough was more common but nasal allergies were less common, in smokers as compared to nonsmoker asthma patients. Further, the mean forced expiratory volume in first second (FEV_1)as well as the mean mini AQLQ scores were lower and the mean ACQ scores, higher in smoker asthma patients as compared to their nonsmoker counterparts ($P<0.05$), indicating that QoL was impaired by smoking in them. With treatment, all the 3 parameters showed significantly higher improvement in TG1 as compared to TG2 ($P<0.05$). Further, higher number of TG1 patients had well controlled asthma and QoL (ACQ score=0.00 to 0.75) as compared to TG2 patients ($P<0.0001$). No serious adverse reaction occurred in any of the patient receiving add on acebrophylline. Control nonsmoker patients showed comparable improvements, even without add on acebrophylline.*

***Conclusion:** Smoking adversely impacts QoL in asthma patients and add on acebrophylline is capable of counteracting the same.*

Keywords: *Smoker asthma patient, Non-smoker asthma patient, Acebrophylline, Quality of life (QoL).*

Introduction

Asthma continues to cause considerable morbidity and mortality, worldwide. Concomitant smoking further increases the disease related morbidity and mortality[1-3] as it alters the underlying airway inflammation in these patients.[4, 5] But the impact of smoking on quality of life (QoL) in asthma patients, is a controversial issue.[6-7] Sharma A et al[7] had observed that acebrophylline was a useful add-on

drug to inhaled corticosteroids (ICS) and long acting beta 2 agonists (LABA) in improving QoL in asthma patients. However, a study observing the effect of add on acebrophylline in smoker asthma patients is not available in English literature to the best of knowledge of the authors.

Aims and Objectives

This study was undertaken to assess:

1) Whether smoking interferes with QoL in asthma patients and

2) If so, whether add on acebrophylline improves the QoL in smoker asthma patients, over and above that caused by ICS and LABA.

Material and Methods

It was a prospective, randomized, single blinded observational study done at the Department of Respiratory Medicine, National Institute of Medical Science & Research, Shobha Nagar, Jaipur, a private, tertiary health care institute, catering lower to middle class rural population of Jaipur district. All adult patients, reporting at the out-patient department with shortness of breath and willing to participate in the study, were recruited for the study (Fig 1). The intake started in January 2015 and lasted up to June 2016. Approval of the Institutional Ethical Committee was obtained for the study [No. NIMSUNI/IEC/2015/2 (889A)]. The study was also registered in Clinical Trial Registry of India (2016/02/010678-ACEBRO-BA).

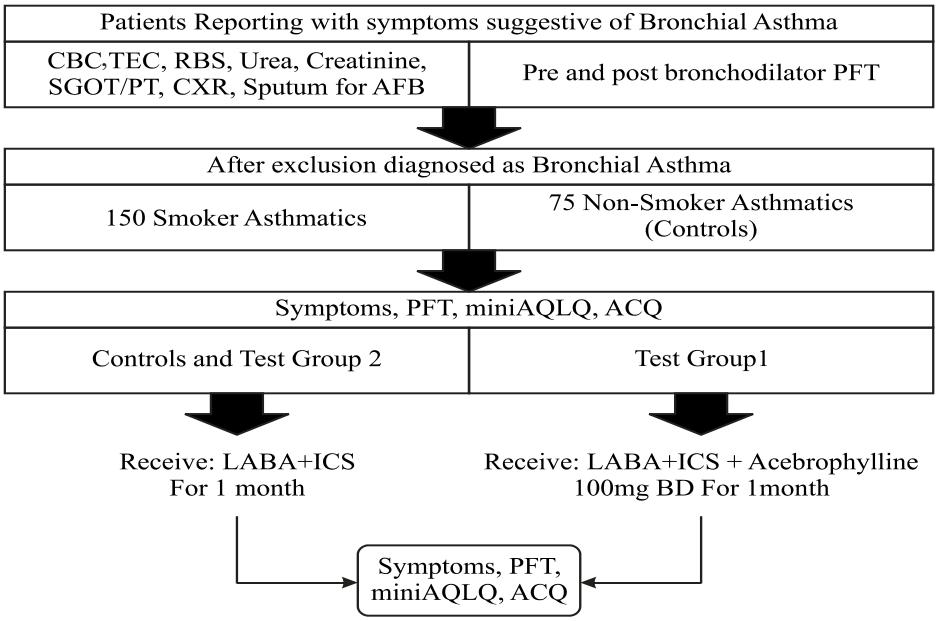


Fig 1. *Flow chart of the study*

These patients were then further evaluated as follows: 1) A detailed clinical history & physical examination, 2) Peripheral blood tests: total/differential blood counts, total eosinophil count, hemoglobin, random blood sugar, urea, creatinine, and liver function tests. 3) 2 sputa for acid fast bacillus (AFB) by Zeihl-Neelson (ZN) method and 4) Skiagram chest posterio-anterior view (PA) view. These patients were also subjected to spirometry using RMS Helios Model 2007-08, Recorder & Medicare systems private limited. Those patients who showed airway obstruction (FEV_1/FVC% <70%) under took reversibility testing using 2 puffs of salbutamol. Bronchial asthma was diagnosed if a patient had 1) Respiratory symptoms suggestive of asthma and 2) Reversible airflow limitation on spirometery (FEV_1/FVC ≤ 70% along with rise in FEV_1 of ≥ 12% and >200 ml).[8]

Out of the total 407 patients so diagnosed as having asthma, those having co-existing diseases like pulmonary tuberculosis, malignancies, diabetes mellitus, hypertension, coronary artery disease, stroke, renal or hepatic failure, were excluded. After such exclusions, all current smoker patients formed the test group patients while the age and sex matched non-smoker asthma patients. (One recruited for every alternate test group patient) served as control. Those patients who were unwilling to bear the cost of travel and/or drugs were also excluded.

Smoking Index (SI) in test group patients was calculated as: Grams of Tobacco smoked per day * No. of years of smoking, where grams of tobacco smoked was assessed as: Number of bidis/cigarettes or 10gm/ number of persons sharing * hookahs/day or 5gm/ number of persons sharing * sulphis#/day. [9]

Informed consent was taken from all the study patients after explaining them the study protocol. They were also advised to stop all the medications they were taking, 24 hours prior to their intake in this study. All the smoker patients were also counseled to stop smoking. The test group patients were then randomly divided into 2 groups: Test Group I (TG1), who received inhaled Fluticasone 250mcg + Formoterol 6mcg as dry powdered inhaler (DPI) along with oral acebrophylline 100mg, twice daily, and Test Group II (TG2), who received inhaled Fluticasone 250mcg + Formoterol 6mcg, as DPI along with oral placebo, twice daily. Control group patients received drugs similar to those received by TG2 patients.

All the study patients were monitored every fortnightly for 1) Control of symptoms, 2) Spirometry, 3) Mini Asthma Quality of Life Questionnaire (mini AQLQ),[10] 4) Asthma Control Questionnaire (ACQ)[11] and 5) Side effects of drugs (Fig 1).

The data so obtained were tabulated and analyzed statistically using $\chi 2$ test, ANOVA, Student t-test/ Fisher's exact test, as and when applicable. A P-value of less than 0.05 was taken to be significant. This study is not funded by any firm or society, therefore there is no conflict of interest.

A sulphi or chillum is a long conical tube made of sand or clay and is used to smoke tobacco in rural India.

Observations and Results

The basic parameters of the study patients are shown in Table 1. The mean age of patients, sex distribution, mean duration of illness, type of smoking, mean smoking index, BMI, symptoms, allergies, mean Post Bronchodilator FEV_1 (PB FEV_1), mean mini AQLQ score and mean ACQ score were similar in the 2 tests groups ($P>0.05$). The controls were age and sex matched. Yet the mean duration of illness was higher, cough was less frequent and nasal allergies more common in controls as compared to the test group patients. Further, the mean FEV_1 and the mean mini AQLQ scores were higher and the mean ACQ scores, lower in them as compared to the test group patients ($P<0.05$). This adverse impact of smoking on mean FEV_1, mean mini AQLQ scores and mean ACQ scores correlated well with smoking index in them (Table 2).

Table 1. *Basic parameters of the patients (n=225)*

Parameter	TG1 (n=75)	TG2 (n=75)	Controls (n=75)	p value
Mean (±SD) age	46.84±11.31	46.81±11.56	46.10±13.00	0.910
Sex Male	62	60	61	0.913
Female	13	15	14	
Mean (±SD) Duration of disease	4.72±2.48	4.62±2.91	5.77±3.83	0.4
Type of smoking				
Bidi	27	26	-	0.9554
Cigarette	05	03	-	
Hookah	43	45		
Sulphi	00	01		
Mean (±SD) Smoking index	224.33±126.13	204.58±109.06	-	0.384
Smoking Index				0.187
≤100	22	18	-	
>100 - ≤300	28	39	-	
>300	25	18	-	
Mean BMI	20.36±3.38	20.67±2.97	20.58±3.27	0.827
Chief Complaints*				
Shortness of breath	75	75	75	0.604
Cough	45	37	25	
Wheeze	62	61	60	
Seasonal Variation	40	41	39	

Other Allergy Symptoms**				
Eye	11	15	13	0.964
Nose	32	28	40	
Skin	09	07	08	
Dust allergy	43	42	44	
Family history	16	14	19	
Mean (±SD) FEV_1	1.49±0.60	1.72±0.51	1.83±0.52	0.041
Mean (±SD) mini AQLQ score***	2.11±0.27	2.18±0.21	2.66±0.20	0.000
Mean (±SD) ACQ score***	4.45±0.52	4.34±0.52	4.13±0.48	0.000

*Several patients had more than 1 complaint

**Several patients had more than 1 allergy

***P value for difference between the 2 test groups (Mini AQLQ; P= 0.060 and for ACQ; 0.209)

Table 2. *Correlation of Smoking index with Mean initial FEV1, mini AQLQ and ACQ*

Smoking Index	Mean FEV_1	Mean mini AQLQ	Mean ACQ
≤100 (N=40) >100 - ≤300 (N=67) >300 (N=43)	1.92±0.55 1.58±0.53 1.36±0.54	2.25±0.21 2.14±0.26 2.05±0.23	4.26±0.49 4.36±0.35 4.60±0.52
F	11.32	6.99	5.26
P value	<.0001	0.0013	0.0062

Thirteen patients in TG1 and 15, in TG2 reformed by 1 month but the remaining 62 and 60 patients in the groups respectively, continued to smoke. The impact of reformation on mean FEV1, mean mini AQLQ scores and mean ACQ scores in them is shown in table 3. It is clear that reformation by itself was not enough to bring significant change in mean FEV_1, mean mini AQLQ scores and mean ACQ scores, at least in short run.

Figures 2, 3 and 4 show the effect on various parameters in the 3 groups on day 0, 15 and 30. All the parameters showed an improving trend from day 0 to day 15 (P<0.05). The mean mini AQLQ score and mean ACQ score showed further improvement from day 15 to day 30 (P<0.05) in all the groups but the mean FEV_1 did not change further (day 15 to day 30) in any of the groups (P>0.05).

Table 3. *The impact of reformation on Mean change in FEV_1, mini AQLQ and ACQ in TG 1 and TG2 patients. (day 0 to day 30)*

Group	Reformation status	Mean change in FEV_1	Mean change in mini AQLQ	Mean change in ACQ
TG1	Yes (13) No (62)	0.38±0.08 0.36±0.10	3.56±0.47 3.57±0.49	-3.59±0.55 -3.67±0.48
	F	0.27	0	0.27
	P value	0.6049	1.0000	0.6049
TG2	Yes (N=15) No (N=60)	0.30±0.08 0.29±0.06	3.38±0.32 3.45±0.28	-3.22±0.50 -3.20±0.51
	F	0.01	0.59	0.04
	P value	0.9206	0.4448	0.8420

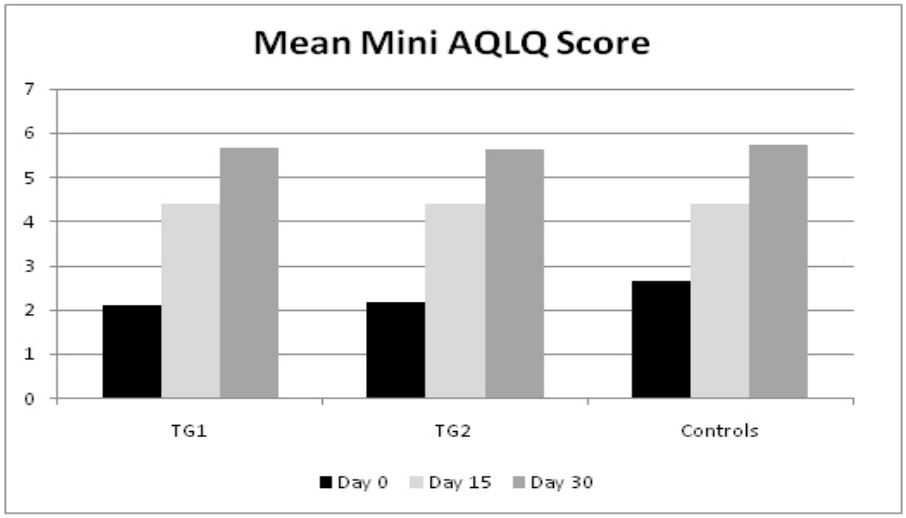


Fig 2. *showing the Mean mini AQLQ on day 0, 15 and 30 in the 3 groups*

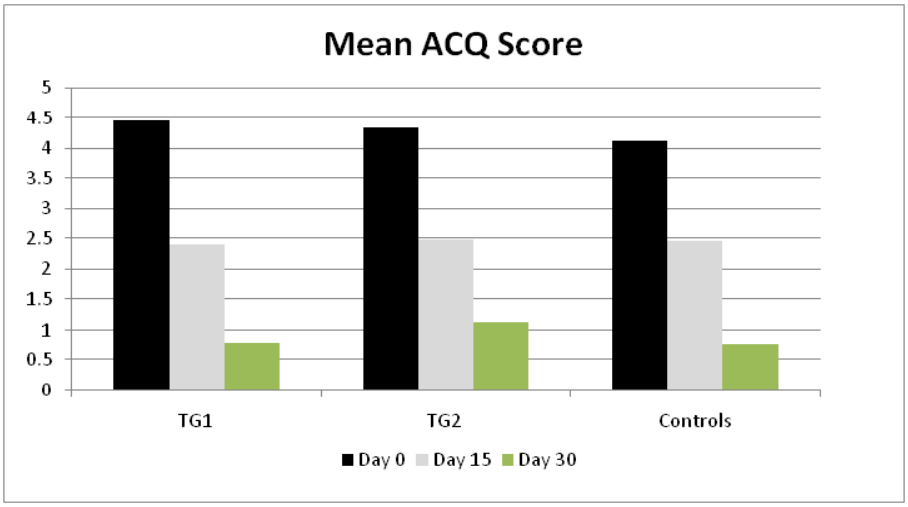


Fig 3. *showing the Mean mini ACQ score on day 0, 15 and 30 in the three groups*

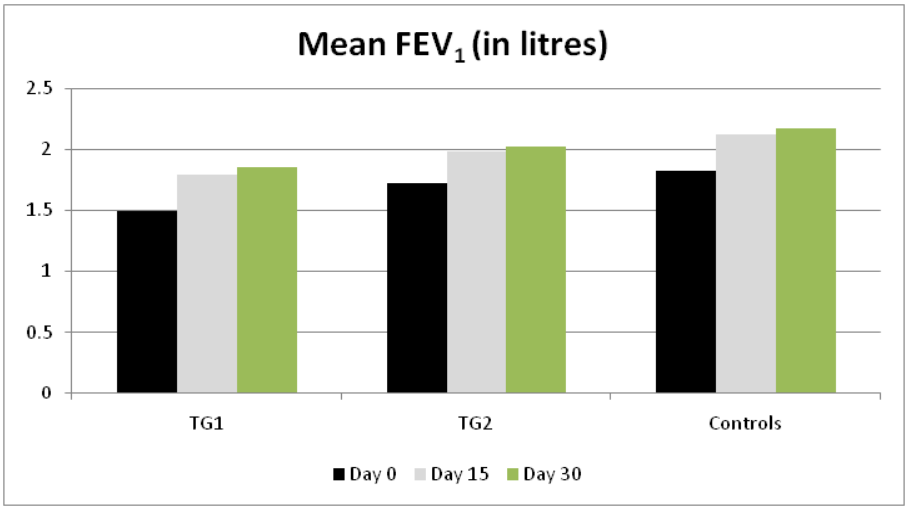


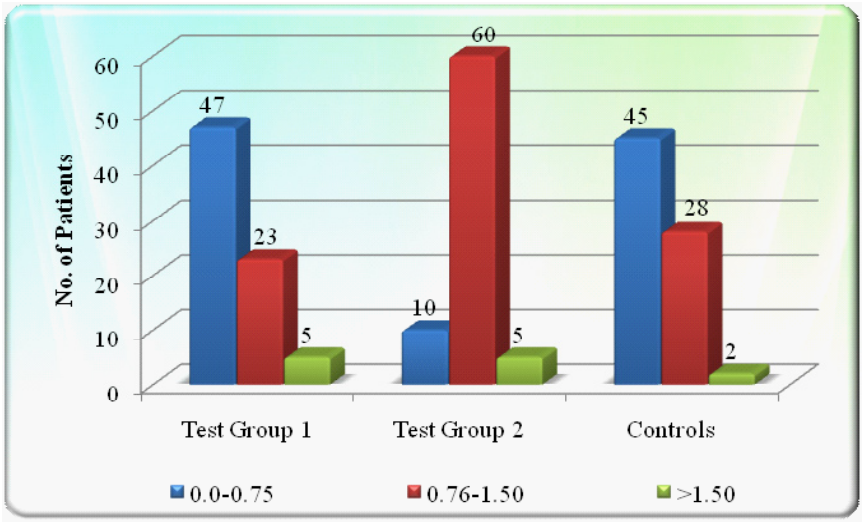
Fig 4. *showing the Mean FEV1 on day 0, 15 and 30 in the three groups*

To further analyze the quantum of impact of therapy in 2 treatment groups, the mean change in different parameters at day 15 and day 30 from its respective values on day 0 and day 15, was also calculated and is shown in Table 4. From this table it is clear that TG1 patients showed significantly higher improvement in all the 3 parameters on day 15 and day 30 from day 0 as compared to TG2(P<0.05).

Table 4. *Mean change in various parameters at Day 15 and Day 30 as compared to the respective values on Day 0 and Day 15*

Parameter	Test Group 1	Test Group 2	t value	P value
Mean Mini AQLQ15-0	2.28±0.18	2.21±0.15	2.593	0.040
Mean ACQ15-0	-2.04±0.55	-1.85±0.47	-2.25	0.026
Mean$FEV_1$15-0	0.30±0.10	0.27±0.05	+2.51	0.013
Mean Mini AQLQ30-0	3.57±0.48	3.05±0.44	+1.99	0.048
Mean ACQ30-0	-3.65±0.49	-3.36±0.51	-5.5	0.000
Mean $FEV_1$30-0	0.36±0.10	0.34±0.18	+4.62	0.000
Mean Mini AQLQ30-15	1.28±0.51	1.23±0.33	+0.8	0.425
Mean ACQ30-15	-1.61±0.49	-1.35±0.41	-3.54	0.001
Mean $FEV_1$30-15	0.06±0.04	0.03±0.03	+5.12	0.000

Figure 5 shows the distribution of final ACQ score of the patients at day 30. Higher number of TG1 and control group patients were placed in well controlled category (0.0-0.75) as compared to that of TG2 group (P<0.0001) showing that add on acebrophylline was capable of reversing the adverse impact of smoking on QoL in smoker asthma patients. Further nonsmoker asthma patients achieved comparable results even without add on acebrophylline.



Chi Sq. =48.75 (p=0.0001)

Fig 5. *Distribution of ACQ scores at Day 30 in patients in the 3 groups*

Table 5 shows the side effects observed during the study period. In all, abdominal discomfort, nausea, palpitation and itching were reported by 2, 2, 1, 1; 1, 2, 1, 1 and 1,1, 0, 0 patients of TG1, TG2 and control patients respectively. All these side effects were of minor nature and self-controlled. Serious side effect requiring withdrawal of drug/s was not reported by any of the patients.

Table 5. *Side effects in the study patients*

Side Effects	TG1	TG2	Controls	Total
Nausea	2	1	1	4
Abdominal Discomfort	2	2	1	5
Palpitation	1	1	0	2
Itching	1	1	0	2
Total	6	5	2	13

Discussion

Although the controls in this study were age and sex matched with test group patients yet cough was more common and the mean duration of illness, lesser common in smoker asthma patients as compared to the controls i.e. the nonsmoker asthma patients. Thus, smoking adversely altered cough and its severity in asthma patients. Siroux et al[1] also noted that current smokers experienced more frequent asthma symptoms than non-smokers. However, nasal allergies were less common in smoker asthma patients than the non-smoker asthma patients of our study. This could be possibly due to more frequent oral inhalations in smokers as compared to nonsmokers or a possible immunosuppressive effect of tobacco smoke on nasal mucosa.

The mean FEV_1, mean mini AQLQ score and mean ACQ score were significantly inferior in smoker asthma patients as compared to the controls (P values <0.05). This clearly shows that smoking adversely impacted pulmonary functions as well as the QoL in asthma patients. This could be further substantiated from the fact that these adverse adverse effects of smoking correlated well with the smoking index in them. Sippel et al,[5] Sharma et al[7] and Tan et al[12] also observed similarly but Boulet et al[6] failed to notice any adverse effect of smoking on QoL in their asthma patients.

From the study data it is also clear that reformation by itself wasn't sufficient to counteract the adverse effect of smoking in these patients, at least in short run. But with therapy patients in all the groups showed significant improvement in mini AQLQ score, ACQ score and FEV_1 values at day 15 of the study (P<0.05). The mean mini AQLQ score and mean ACQ score showed further improvement from day 15 to day 30 (P<0.05) but the change in mean FEV_1 from day 15 to day 30 for all the 3 groups was statistically insignificant (P>0.05). Further, it was also observed that TG1 group patients who received add on Acebrophylline, showed significantly higher changes in all the 3 parameters i.e. mean mini AQLQ score, mean ACQ score and mean FEV_1 value, as compared to TG2 patients at day 15 &day 30 (P<0.05). This was possibly due to the "add on anti-inflammatory effect" of acebrophylline in the smoker asthma patients.

GINA guidelines-2016[8] have included ACQ scores to grade the response to treatment. We found that post treatment, 47 and 45 patients respectively from TG1 and controls were well controlled (0.0-0.75) as compared to only 10 patients in group TG2. This clearly shows that "add on acebrophylline" is capable of counteracting the adverse effect of smoking on asthma control and thereby QoL in asthma patients, over and above that caused by ICS and LABA but the latter drugs were capable of causing similar level of improvement in controls, even without "add on acebrophylline".

In our study, add on acebrophylline was not associated with any serious toxicity profile. Tapadar SR et al[13] also found that while epigastric tenderness, nausea and headache were common in their patients treated with acebrophylline, cardiovascular system related complaints e.g. pain chest, palpitation, tremor, tachycardia or insomnia and sleep disorders were very uncommon.

Conclusion

From the results of this study, it can be safely concluded that smoking adversely impacts symptoms, pulmonary functions and QoL in asthma patients, these adverse effects of smoking cannot be reversed by simple reformation only, at least in short run but add on acebrophylline is capable of improving pulmonary functions as well as QoL in these patients, over and above to that caused by ICS and LABA. However, large scale clinical trials are required to substantiate the above findings of this study.

References

[1] Siroux V, Pin I, Oryszczyn M, Moual NL, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. European Respiratory Journal.2000;15:470-477.

[2] Ulrik CS, Lange P. Cigarette smoking and asthma. Monaldi Archives For Chest Diseases. Aug 2001; 56:349-53.

[3] Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, Jindal SK et al for Asthma Epidemiology Study Group. Prevalence and Risk Factors for Bronchial Asthma in Indian Adults: A Multicentre Study. The Indian Journal of Chest Diseases & Allied Sciences. 2006;48:13-21.

[4] Pedersen B, Dahl R, Karlstrom R. Eosinophil andneutrophil activity in asthma in a one-year trial with inhaled budesonide: the impact of smoking. American Journal of Respiratory and Critical Care Medicine. 1996; 153:1519-1529.

[5] Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML. Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. CHEST. 1999;115:691-6.

[6] Boulet LP, Lemière C, Archambault F, Carrier G, Descary MC, Deschesnes F. Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. CHEST. 2006;129:661-8.

[7] Sharma A, Adiga S, Chogtu B, Mohapatra AK, Magazine R. Comparing the efficacy and influence on the quality of life of three classes of drugs used in bronchial asthma-A prospective study. Journal of clinical and diagnostic research: JCDR. 2014; 8:HC13.

[8] Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2016. Available from: http://www.ginasthma.org/. Retrieved on 24th March, 2016.

[9] Jindal SK, Malik SK. Smoking Index-A method to quantify cumulative smoking exposure. Lung India. 1988;4:195-196.

[10] Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. EurRespir J. 1999;14:32-8.

[11] Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. EurRespir J. 1999;14:902-7.

[12] Tan NC, Ngoh SHA, Teo SSH, Swah TS, Chen Zan, Tai BC 'Impact of cigarette smoking on symptoms and quality of life of adults with asthma managed in public primary care clinics in Singapore: a questionnaire study', Primary Care Respiratory Journal. 2012;21:90-93.

[13] Tapadar SR, Das M, Chaudhuri AD, Basak S, Mahapatra ABS. The Effect of Acebrophyllinevs Sustained Release Theophylline in Patients of COPD- A Comparative Study. Journal of Clinical and Diagnostic Research. 2014; 8:MC11-MC14.

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